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Measures of Exposure to Environmental Tobacco Smoke

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Validity, Precision, and Relevance

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ABSTRACT: **It is often not clear what the best measures of exposure are for a risk assessment, or even how one should answer this question. Environmental tobacco smoke (ETS) provides a good example for an exploration of uncertainty. There are a variety of methods for estimating exposure and each has shortcomings. In this paper we summarize the physical characteristics of ETS and the principal methods for assessing exposure. We review the accuracy and applicability of these methods, and explore major sources of uncertainty in the assessment of ETS.**

INTRODUCTION

Environmental tobacco smoke (ETS) is a good example for any consideration of uncertainty in risk assessment. Exposure is widespread, occurring in workplaces and in general environmental settings. The topic has been closely studied, but much is still not known about the characteristics of ETS and its effects on health. Relative risks associated with ETS are modest, are certainly smaller than those related to active smoking, and they increase the importance of accuracy in exposure assessment. The potential social implications of ETS risk assessments are huge—smoke free policies may affect all work sites and enclosed public spaces. The tobacco industry regards ETS as a serious threat to its own commercial interests,[1] consequently, the industry funds and promotes its own reviews that, on the whole, emphasize the shortcomings of the scientific case against ETS.[2] For all these reasons, there is keen public interest in the nature and extent of uncertainties in ETS risk assessment.[3]

WHAT IS ENVIRONMENTAL TOBACCO SMOKE?

ETS is made up mostly of so-called sidestream smoke, which passes directly from the glowing tip of the cigarette into the environment. Small contributions stem from other sources, including exhaled mainstream smoke. The chemistry and distribution dynamics of ETS are complex. We focus on the major characteristics of ETS that are relevant to exposure assessment and calculation of health risks.

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ETS includes thousands of compounds, the levels of which depend on the way the cigarette is smoked and its composition. For example, puff volume and puff frequency determine the proportions of ETS made up by glow and smoulder stream smoke. Sidestream to mainstream ratios depend on the compound that is measured, the way the cigarette is smoked, and the quantity of tobacco made available for combustion. In general, sidestream smoke is produced at lower temperatures, and in less oxygen-rich conditions, than mainstream smoke. As a consequence, the products of combustion differ. For example, sidestream smoke contains more CO and less CO_2, and higher levels of combustion products formed by nitrosation and amination. Within a short distance of a burning cigarette ETS is largely undiluted, and exposure to potentially harmful smoke components is likely to be heavier and more uniform than in the case of *distant* passive smoking.

The age of ETS influences the balance of semivolatile constituents between vapor and particulate phases. Some compounds are rapidly oxidized. Others (such as nicotine) are in equilibrium between vapor and gas phases, and are affected by dilution of the smoke and changes in temperature and humidity. In mainstream smoke (and fresh sidestream smoke) nicotine is held on the surfaces of droplets but, with air dilution, most of the nicotine evaporates.[4]

Sidestream smoke is less acidic than mainstream smoke (pH about 7, compared with pH about 6 for mainstream cigarette smoke).[4] This is due chiefly to the much higher levels of ammonia in undiluted sidestream smoke. As a result, nicotine is present in greater quantities in the unionized form, in which it is more readily absorbed by the body.

The size of particles in sidestream smoke varies with many factors, including the age of the smoke, ambient temperature, and humidity. Overall the particles tend to be smaller than those present in mainstream smoke,[4] resulting from the evaporation of semivolatile constituents. Due to their size (mostly between 0.1–0.4 μm in diameter) the particles are distributed rapidly by convection currents throughout a room or any other closed space.

The number of people in the mixing space and their level of activity influence the rate of adsorption of smoke constituents and the circulation of smoke particles, as do the physical characteristics of the indoor environment, such as the presence of furniture, drapes, and carpets.[5] The dispersion and decay of ETS occurs at different rates for different constituents. Levels of particulate matter in the atmosphere are likely to fall more quickly than do levels of gaseous smoke products. Reactive components (such as NO_2) decay more rapidly than more stable compounds (for example, CO).

The deposition of smoke particles is influenced by characteristics of the smoke (particle size most importantly) and by biological variables concerned with manner of inhalation and the configuration of the respiratory tract. The fraction of ETS particles deposited in the respiratory tract is estimated to be between 10–20%.[6] By contrast, 70–90% of particles in mainstream smoke inhaled by smokers are deposited in the respiratory tract.[7] The proportion of ETS deposited in the lungs of a child may be considerably higher than for an adult due to differences in the diameter and configuration of the airways. Studies of air flow and aerosol deposition in models of infant lungs have found that the total deposition is up to 50% greater than in adult lungs, with proportionately heavier deposits in the tracheobronchial area.[8]

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WHY DO WE NEED GOOD MEASURES OF EXPOSURE TO ETS?

In etiologic studies, estimation of the risk of disease associated with ETS depends on accurate measurement of exposure. The extension of biomarker studies to measures of early biological response, such as carcinogen-hemoglobin adducts, contributes biological plausibility to epidemiological studies of cancer and ETS. This may in future add to our understanding of the mechanisms of disease.[9] The accuracy of measures of exposure is particularly important when the relative risks are modest in magnitude and the results of the studies have substantial policy implications.

At the population level, measures of exposure are necessary for estimating the burden of disease that is attributable to ETS, and to guide public health policy. For example, in many countries 30–40% of children are exposed to smoke in the home and, consequently, a substantial proportion of cases of common childhood illnesses may be attributed to ETS. In Australia, it is estimated that 2,330 hospital admissions

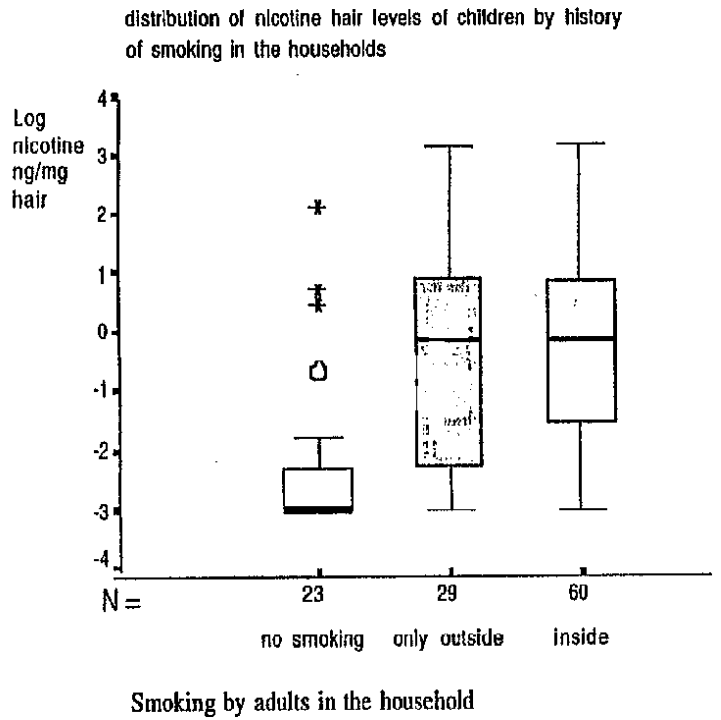

FIGURE 1. Hair nicotine levels in New Zealand children whose parents reported they were nonsmokers, smoked only outside the house, or smoked indoors. (Source: Al-Delaimy *et al.* Ref. 12.)

per year, or 13% of all admissions for lower respiratory illness in the first 18 months of life, are due to exposure to parental cigarette smoke in the home.[10]

Measures of exposure are needed to study the effect of interventions that reduce ETS. For example, questionnaires and cotinine measures have been used to assess the outcome of health education programmes that encourage parents to reduce exposure of children to ETS.[11] More than one method may be required to obtain an accurate picture of exposures. A recent study in Wellington found that children of parents who reported that their house was smoke free had similar levels of nicotine in their hair as did children whose parents reported that they smoked inside the house, suggesting that parents inaccurately report their smoking habits, either that or smoke free homes make little difference to childhood exposure to ETS in New Zealand[12] (see FIGURE 1).

Other examples of exposure assessment include physically monitoring smoking in specific workplaces,[13] and national surveys to track the effect of smoke free legislation.[14]

HOW CAN EXPOSURE TO ETS BE MEASURED?

Questionnaires

Questionnaires are the most commonly used method of exposure assessment in studies of the health effects of ETS (see TABLE 1). Advantages include the ability to provide detailed information on ETS source strength, retrospective exposure information, measures of exposure over an extended period, and simultaneous information on time-activity patterns and modifying environmental factors. Questionnaires provide information at relatively low cost, which is important for studies that require large sample sizes.[15]

The principal disadvantage of this method of assessment is the susceptibility of questionnaires to misclassification. In the case of active smoking, the number of cigarettes smoked by an individual is commonly accepted as providing a reasonable quantitative index of exposure to tobacco smoke. However, ETS exposure cannot be simply related to the number of cigarettes smoked by others.[16] Many other variables are important, such as the size of the space, amount and quality of ventilation and crowding. The breathing and smoke-puff patterns of the smoker, the proximity to the source of ETS, and the precise time spent in a room in which smoking has occurred are variables that cannot be readily accounted for in questionnaires. Low-level exposures may be overlooked: biomarker studies show that tobacco-specific substances such as nicotine and cotinine are frequently present in blood, urine, and saliva of people who report that they are not aware they have been exposed to ETS.[17] Even more troublesome is the potential for systematic errors in exposure assessment by questionnaire. For example, growing awareness of the hazards of passive smoking to health, and possibly a social stigma associated with exposing others (especially children) to ETS, may lead to differential under-reporting.[18]

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TABLE 1. Methods of exposure assessment used in studies of health effects of passive smoking (see Ref. 10)

Health effect	No. of studies[a]	Exposure questionnaire	Exposure biomarker	Exposure questionnaire and biomarker
low birth weight (due to maternal exposure to ETS)	18	15	2	1
childhood asthma	68	64	1	3
lower respiratory illness in first 18 months	47	44	1	2
lung function in childhood	25	19	3	3
sudden infant death syndrome	8	8	—	—
middle ear disease in childhood	19	17	2	—
lung cancer	40	39	—	1
major coronary events	17	16	—	1

[a]Drawn from peer-reviewed literature published before July 1997.

Biological Markers

The major advantage of biomarkers is the ability to measure an absorbed dose of ETS rather than the potential dose (exposure) in the external environment. Biomarkers are said to be *objective*. This is not true, since any method of measurement requires some degree of judgement. However, biomarkers might be regarded as less subjective than questionnaires in the sense that they rely on the discretion of the investigator alone. Choices must still be made. For instance, the selection of analytic method involves a trade-off among sensitivity, specificity, cost, and acceptability. Measurement of cotinine in urine by radioimmunoassay (RIA) is cheaper than measurement by chromatography, but RIA is less specific due to cross-reactions with other nicotine metabolites.[16] Mass spectroscopy is the most accurate technique of all, but this is considerably more expensive than the alternatives. The quantitative aspect of measurement by biomarker is attractive, but the appearance of precision may be misleading. Absorption, distribution, storage, metabolism, and elimination of nicotine and cotinine in human bodies, for example, are not fully understood, adding uncertainty to the interpretation of test results, which may be compounded by inter-laboratory variation.

Most recent work on biomarkers for ETS has been based on nicotine and its metabolites (especially cotinine), because of the high degree of specificity of these substances for exposure to tobacco smoke. (Although there are other sources of nicotine, such as fruit and vegetables, the contribution is negligible except in extreme circumstances. Benowitz[16] estimates that to reach a level of cotinine typically seen following ETS exposure, a person would need to consume each day more than 4.6 Kg of cauliflower or 7.6 Kg of tomatoes.) The principal advantage of cotinine measurement over nicotine in body fluids is its greater persistence in the body—the halflife of cotinine is 20–24 hours, compared with two hours for nicotine. In addition, a range of DNA and protein adducts and other carcinogen biomarkers have been identified in nonsmokers, with levels related to self-reported exposure to ETS.[9,19] Difficulties in applying these measures to risk assessment include lack of specificity (due to environmental sources other than tobacco smoke) and the high cost of many of the analyses.

Cotinine is the major proximate metabolite of nicotine that can be measured in urine, serum, saliva, other body fluids, and hair.[16] Levels of exposure to ETS in the home, as assessed by the reported smoking habits of the family members, have been correlated with urinary cotinine levels of children[20,21] and nonsmoking adults.[22] Limitations apply chiefly to the duration of exposure that is recorded, and the uncertain relation between cotinine levels and the biologically effective dose or doses of ETS constituents that are relevant to the disease under study. Cotinine is itself biologically inert and is formed principally by oxidation of nicotine in the liver. Consequently, measures of cotinine may provide an imperfect reflection of significant *upstream* exposures, such as those impacting on the respiratory mucosa. Since the ratio of nicotine to other components of ETS varies with many factors, such as the age of the smoke, spot measures of cotinine may misrepresent the levels of other constituents that are absorbed. The half-life of cotinine means that, at most, measures refer to several days of past exposure to nicotine. Moreover, there is considerable between-individual variability in the proportion of nicotine metabolized to cotinine (ranging between approximately 50% and 90%) and the rate at which cotinine is metabolized.[16,23] Cotinine clearance varies with factors such as ethnicity, sex, and age.[16] Children tend to have higher cotinine levels in urine than adults for similar exposures to ETS. This may be due to age-related differences in nicotine metabolism, or to higher doses of ETS resulting from higher relative ventilation rates among children.

Recently, the search for more stable measures that avoid some of the disadvantages encountered with testing of body fluids has led to the investigation of hair as a biomarker for ETS. Each centimeter of hair reflects approximately one month of exposure, since hair has a fairly uniform growth rate (1.0 ± 0.3 cm per month.[24] Nicotine in hair is derived mainly from nicotine in blood, although some may be absorbed directly from the atmosphere.[25] Cotinine is present in hair, but at much lower concentrations than nicotine. Both compounds are preserved in the shaft throughout the life of the hair and, after cutting, samples can be stored at room temperature for years within a closed envelope without loss or degradation of hair nicotine.[26] Among active smokers, the centimeter-by-centimeter distribution of nicotine corresponds moderately well with average month-by-month number of cigarettes smoked.[24] Among nonsmokers, several studies have reported that the method is sufficiently sensitive to be able to detect changes in ETS exposure and to differentiate people according to their levels of exposure.[26] In one study of children, nicotine in hair correlated more closely with smoking history of parents of exposed and unexposed children than did cotinine in urine.[27]

There are many possible causes of between- and within-individual variation of uptake of nicotine into hair, including variable reporting of exposure history, differences in ventilation, exposure time, and distance from the source of exposure.[21]

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Moreover there are confounding factors specific to hair, such as irregular hair growth, diffusion, and washing out of nicotine following application of bleaches and dyes. Hair color is also relevant: black hair tends to contain higher levels of nicotine than fair hair for similar exposures to ETS.[29]

Environmental Measurements

Components of ETS that may be monitored in the environment include nicotine, particulates, and a number of gases. Recently studies have examined the value of solanesol, a tobacco leaf constituent present in cigarette smoke condensate.[10] Its utility lies in its abundance, lack of volatility, and lack of any indoor sources other than tobacco.

Environmental measurements may be obtained by stationary air sampling monitors, personal sampling with pump driven nicotine or respirable suspended particulate samplers, or personal sampling with a diffusion-based nicotine sampler. Using these methods it has been shown that the number of smokers in a household has a strong effect on indoor levels of respirable suspended particulates (RSP)—a pack-a-day smoker adds approximately 15–20 $\mu g/m^3$ to typical household levels, which is similar to RSP concentrations observed in outdoor air in some cities.[30] Personal monitors provide more direct measures of ETS exposure than stationary samplers, but there are obstacles to applying this technique in large scale surveys. Generally these environmental monitors can be used for short time periods only, which may be sufficient for some purposes (such as comparisons of workplaces with and without smoking policies) but is less helpful in studies of disease etiology. However, passive monitors may be used to check the accuracy of questionnaires which are applied subsequently to measure exposure in large scale surveys.

VALIDITY, PRECISION, AND RELEVANCE IN ASSESSMENT OF ETS EXPOSURE

The validity of an exposure measure is a function of bias (average measurement error) and precision (variability in measurement error). In the absence of a "gold standard" measurement of true exposure, the extent of bias and imprecision can only be estimated by making comparisons between different measures of exposure.

Questionnaire assessments of exposure to ETS often rely on self-reported smoking (for example, parents reporting on smoking in the home during studies of ETS and children). The accuracy of self-reported smoking depends on the circumstances under which the information is elicited. Patrick *et al.*[31] reviewed 26 studies in which questionnaire responses had been compared with biochemical measures of smoking. On the whole, the different measures of smoking were consistent, but the extent of agreement varied widely. Treating the biochemical measures as a reference, sensitivity ranged from 6% to 100% (mean 87.5%) and specificity from 33% to 100% (mean 89.2%). The wording of the questionnaire and the context in which questions were asked were important: higher estimates of sensitivity and specificity were observed when the questionnaire was administered by an interviewer, for observational studies rather than interventions, when adults answered rather than adolescents, and

when the biochemical assessment was by cotinine rather than other markers (such as nicotine or exhaled CO).

The reliability of ETS exposure estimates may be tested by repeating questionnaires that refer to a particular period, or repeating biochemical measures on the same sample. On retesting, questionnaires do well in terms of broad categories of *presence* or *absence* of exposure. For example, in an Australian study mothers were asked about smoking during the first year after delivery; 97.7% gave the same answer ("yes" or "no") as they did two months earlier.[32] Questions on the extent of exposure are less reproducible. A study of lifetime exposure to ETS of adult nonsmokers in New Mexico found a high degree of agreement between two interviews within six months (more than 90%) for parental smoking during childhood but much lower figures for amount smoked or hours of exposure.[33] Similarly when Pron *et al.*[34] reinterviewed 117 subjects after six months, good agreement was found for reports of occupational and residential ETS exposure, but the reliability of reported duration of exposure was poor. Within-sample variability in biochemical measures of exposure to ETS should be low for a given laboratory; variability between laboratories is seldom reported.

Repeated tests of biomarkers and environmental measures of ETS show considerable within-individual variation. Coultas *et al.*[35] reported that indicator variable for self-reported exposure explained no more than 6–10% of the variability in atmospheric monitoring, and 18–20% of variability in urinary and salivary cotinine levels. It is difficult to know how much of this unexplained variation is due to underlying variability in the true exposure, and how much is due to measurement error. Repeated measures improve the characterization of an individual's exposure to ETS, but single measures may be sufficient to distinguish between groups that are *exposed* or *unexposed* (or, more accurately, *more exposed* or *less exposed*). Henderson *et al.*[36] reported that levels of nicotine in air and cotinine in urine fluctuate widely on retesting, but the ranking of individuals from one test to another was less variable, and both air nicotine and urine cotinine measures consistently distinguished *exposed* households (those containing smokers) from *unexposed* households (those without smokers).

Which measures of exposure to tobacco smoke best predict health outcome? Bias aside, the most accurate measure of exposure should be associated with the strongest measure of effect (assuming that an effect does exist).

Few studies have reported risk estimates based on measures of exposure other than questionnaires. In addition to those listed in TABLE 2 (passive smoking) and TABLE 3 (active smoking), de Waard *et al.*[37] compared questionnaires and urine cotinine levels in relation to incidence of lung cancer in a cohort of women, but the data are not reported in full. In this study, after up to 15 years of followup, 23 incident cases were identified among nonsmokers. ETS exposure to the time of enrollment was compared with controls chosen from within the cohort. The odds ratio for the nonsmokers in the top tertile of cotinine compared with the bottom tertile was 3.3 (0.7–8.3). No comparable results were reported for the questionnaire results, but the paper noted, for active smokers, that "lung cancer distribution between different levels of self-reported cigarette consumption did not differ significantly from [the distribution across] corresponding cotinine categories". Wang *et al.*[38] reported a clear inverse dose-response association of cotinine in maternal urine during pregna

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TABLE 2. Health effects of exposure to ETS from studies reporting results using both questionnaire and biomarker assessments of exposure

Reference	Study population	Health outcome	Exposure measure	Measure of effect
Ehrlich *et al.*[50]	72 children 3–14 years, attending emergency room with acute asthma, 121 emergency room controls	emergency room treatment for acute asthma	(1) maternal caregiver smokes: yes vs. no	odds ratio = 2.0 (1.1–3.4)
			(2) urine cotinine: ≥ 30 ng/mg creatinine vs. < 30 ng/mg	OR = 1.9 (1.0–3.4)
Chilmonczyk *et al.*[51]	199 asthmatic children aged 8 months to 13 years	acute exacerbations of asthma	(1) No. of care-givers who smoke: mother and others vs. none	ratio = 1.8 (1.4–2.2)
			(2) urine cotinine: 40+ ng/ml vs. < 10 ng/ml	ratio = 1.7 (1.4–2.1)
Rebagliato *et al.*[52]	710 nonsmoking pregnant women	mean birthweight	(1) h/week reported exposure to ETS: 42+ (top quintile) vs. none	deficit = 88 g
			(2) maternal serum cotinine: 1.8+ ng/ml (top quintile) vs. < 0.5 ng/ml	deficit = 98 g
Rylander *et al.*[53]	112 hospital cases aged 4–18 months, 196 population controls	hospital admission for wheezing bronchitis	(1) number of parents who smoke: both vs. none	OR = 2.0 (1.1–3.7)
			(2) urine cotinine: 10+ µg/L vs. < 2.5 µg/L	OR = 2.1 (1.1–4.6)
Tunstall-Pedoe *et al.*[54]	population sample of 986 men and 1492 women aged 40–59 years	prevalence of diagnosed coronary heart disease	(1) reported exposure to ETS: *a lot* vs. *none*	OR = 2.4 (1.1–4.8)
			(2) serum cotinine: > 4 ng/ml vs. < 0.01 ng/ml	OR = 2.7 (1.3–5.6)

TABLE 3. Health effects of active smoking from studies reporting results using both questionnaire and biomarker assessments of exposure

Reference	Study population	Health outcome	Exposure measure	Measure of effect
Haddow *et al.*[55]	4211 pregnant women providing a blood sample at 15–21 weeks gestation	birth weight	(1) self-reported no. of cigarettes smoked per day: top 2.7% (25+) vs. nonsmokers	mean difference in birth weight −289g
			(2) serum cotinine: top 2.7% (284 ng/ml) vs. < 24 ng/ml	−441g
Woodward *et al.*[56]	79 mothers of children in top quintile of frequency of respiratory illness in first 18 months of life, compared with 72 mothers of children in bottom quintile	prone to acute respiratory illness in childhood	(1) self-reported smoking in mid-trimester of pregnancy: yes vs. no.	OR = 1.50 (0.73–3.08)
			(2) cotinine in serum collected at 16–20 weeks gestation: 57+ nmol/L vs. < 57 nmol/L	OR = 1.72 (0.83–3.50)
Perez-Stable *et al.*[57]	743 adults participating in national nutrition survey	acute biochemical and physiological changes	(1) self-reported number of cigarettes smoked per day- (2) serum cotinine	cotinine more strongly correlated with hematocrit, hemoglobin, white cell count and diastolic blood pressure

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and infant size at birth. The relation with maternal self-reported smoking was less striking. Surveys of passive smoking and lung function in children found that salivary cotinine and questionnaire estimates of exposure were similarly associated with small decrements in most spirometric indices.[39,40]

These comparisons should be treated with caution. The definitions of exposure are to some extent arbitrary (for example, there is no fixed cut point for serum cotinine that distinguishes an active smoker from a nonsmoker heavily exposed to ETS) and may be made *post hoc*. Consequently results are susceptible to reinterpretation and, possibly, reporting bias. Questionnaire and cotinine measures of exposure do tend to be correlated,[40] indicating that to some extent the two approaches measure common events. One would expect questionnaires to have greater predictive validity when the relevant exposure occurred in the distant past (for example, in case control studies of cancer), whereas cotinine measures are likely to be more strongly related to acute outcomes, but this is not apparent in TABLE 2. Perhaps the most likely reason for these findings is that the two approaches are similarly imperfect, although the source and nature of the errors differ. Assuming that the errors in biomarkers and questionnaires are not correlated, consistency in the risk estimates supports the validity of both methods of exposure assessment.

The question of which is the *best* measure of exposure of ETS must take account of operational issues, such as acceptability and cost. The cost of the different methods of exposure assessment varies widely. For example, hair nicotine testing may add $30–100 per participant (depending on the method of analysis) to the cost of questionnaires. This means that possible gains in precision and face validity and reductions in systematic error must be weighed against the loss of statistical power that occurs if the number of study participants needs to be limited. The acceptability of collecting biological samples may also be an issue in some populations. For example, most cultures have restrictions of some kind on the cutting of hair. Some groups strictly prohibit cutting the hair of young male children: other cultures restrict the time of day at which hair may be cut.

WHAT ARE THE MAJOR SOURCES OF UNCERTAINTY IN ASSESSMENT OF ETS?

Uncertainty has many meanings and arises from multiple sources; sometimes it results from a lack of information, and on other occasions it is caused by disagreement about what is already known. Some categories of uncertainty are amenable to quantification; others defy numerical boundaries and probabilities.

Morgan and Henrion[41] proposed these sources of uncertainty in risk assessment:

- linguistic imprecision
- statistical variation
- variability
- approximation
- subjective judgement
- disagreement.

Ambiguity in language certainly contributes to confusion and misunderstanding in exposure assessment of ETS. For example, the term *ETS* may refer to undiluted smoke emitted directly from the cigarette, or to aged and diluted smoke, which has quite different characteristics. As in other areas of science, commonly-used phrases such as "the weight of the evidence" and "adequate data" mean quite different things depending on the perspective of the author; a small number of studies becomes "several" or "a few" depending on whether or not the studies are being cited as supportive evidence.

In this instance, statistical variation, which is well understood and relatively straightforward to describe and allow for, poses less of a problem for risk assessment than does the underlying variability in exposures. The nature of ETS, with intermittent releases and many factors in the chain between source and biologically effective dose, virtually ensures that uncontrolled variability will be high.

TABLE 4. Issues for which the experts disagree—uncertainty in risk assessment of ETS

	Risk-tolerant view	Risk-sensitive view
extrapolating from home exposures to work exposures	most work exposures much less than in home with one or more smokers	in high exposure settings, work exposures comparable to heavy ETS exposure at home
risk estimates	emphasize small relative risks	emphasize substantial attributable risks
confounding and bias	focus on potential for unrecognized or uncontrolled errors	focus on factors that have already been controlled
biological mechanisms	biological plausibility a high priority in determining causation	plausibility a soft criterion for causation
heterogeneity in exposures and study designs	assumed to be high	assumed to be sufficiently low to justify pooling results
what constitutes acceptable quality of evidence	more demanding—quality of the science is the only consideration	less demanding—severity of problem requires decision
variability in exposure measures	emphasize differences between individuals	emphasize differences between groups
analogy with active smoking	depending on implications for risk—differences or similarities emphasized	depending on implications for risk—similarities or differences emphasized
exposure to ETS represented as cigarette-equivalents	cite cigarette-equivalents of nicotine	cite cigarette-equivalents of substances with higher ETS: mainstream ratios than nicotine

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Approximation is a cause of uncertainty when processes are complex and simplifying assumptions must be made. For example, the use of biomarkers in ETS exposure assessment is based on assumptions about the biological mechanisms of action, although it is not clear at present which components of ETS are most important in the etiology of disease. Cotinine measures are used in studies of ETS and heart disease, for example, although it is not clear whether the cardiotoxic components of ETS are gaseous or particulate, whether nicotine is directly relevant, or what period must elapse between exposure and presentation of disease.

Bridging data gaps such as these requires judgement, and differences in judgement are a common cause (although not the only one) of disagreement. We searched the literature on ETS to identify common disagreements, and characterized these in terms of *risk tolerant* (slow to concede that ETS causes health risks) and *risk sensitive* (quick to claim that ETS is a health risk) positions (see TABLE 4).

The tension between the risk tolerant and risk sensitive points of view affects exposure assessment in many ways. For example, the definition of an *acceptable quality of evidence* determines which data are included in assessments, and which are excluded.[42] Accepting or excluding studies for pooled analyses also depends on judgement, in this instance assessment of the degree of heterogeneity in study design.

When considering the use of cotinine and nicotine as measures of ETS exposure, emphasis on variations between individuals[23] leads to a higher estimate of uncertainty than is apparent from a perspective that concentrates on comparisons between groups.[16] In a similar vein, the *risk tolerant* perspective on ETS in the workplace emphasizes the low exposures that individuals receive (on average), and the small increase in personal risk that may result.[43] The *risk sensitive* perspective takes a population-wide view and emphasizes the substantial burden of illness that results from a widespread exposure.[17] Commentators who are *risk tolerant* emphasize the differences between active and passive smoking (e.g., dilution, particle size, and lung clearance) when considering the question of whether ETS is hazardous.[44] The *risk sensitive* perspective on the same question highlights similarities (e.g., the presence of proven carcinogens in both mainstream and sidestream smoke).[4] Interestingly, the positions are somewhat different with regard to risk assessment. Those who hold that there is a minimal (or nonexistent) risk sometimes support this position by linear extrapolation from the effects of active smoking, using the notion of *cigarette equivalents* of ETS exposure.[45] Those who believe that there are indeed nontrivial risks from ETS argue that ETS may differ significantly from active smoking in its mechanisms of action (in, for example, its greater than expected effect on the progression of atherosclerosis[46]). The idea of cigarette-equivalents is itself an ambiguous one, since the magnitude of the imputed exposure to ETS depends very strongly on which compound is chosen as the index.[6]

Disagreement also results from differences due to factors such as career expectations, disciplinary background, and economic interests. A study of reviews of ETS for example, found that an article produced by authors with affiliations to the tobacco industry was 88 times more likely to conclude that passive smoking is not harmful, than articles written by authors with no connections to the industry.[47] Such a divergence of views on a common data set is not peculiar to ETS. Brunk *et al.*[48] describe the different pathways taken in Canada by industry, government, and an independent

inquiry to the risk assessment of the pesticide alachlor; and van Asselt *et al.*[49] describe how various world views affect estimates of the impact of population growth on human health. Differences among perspectives are to be expected and should not paralyze the decision-making process. Disagreement and uncertainty are not, on their own, sufficient reasons for failing to act to reduce risks to health.

CONCLUSIONS

Whether or not a measure of exposure is sufficiently accurate depends on its purpose. For public health and regulatory purposes, such as the monitoring of smoke-free policies, simple questionnaires are effective measures of exposure to ETS. Studies of disease etiology may require more discriminating measures. None of those that are presently available provide a comprehensive, long-term picture of individual exposures to ETS. However, questionnaires and cotinine measurements may provide satisfactory instruments for epidemiology studies, which aim to distinguish groups in terms of the magnitude of exposure to ETS. There are still uncertainties associated with the assessment of ETS. Some of these are due to missing data and will be overcome when more is known about ETS. However, uncertainty is also a consequence of differing values and expectations that scientists and commentators bring to the analysis and interpretation of the data.

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The Contribution of Environmental Monitoring in the Epidemiological Assessment of Exogenous Risk

The Experience of ARPA in the Emilia-Romagna Region of Italy

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ABSTRACT: **The aim of the Emilia Romagna-Region Agency for Prevention and Environment (ARPA) is to define and improve interactions among the various prevention departments of the Emilia-Romagna Local Health Authorities in order to attain better knowledge about the health status of the population by using epidemiology and etiology studies, as well as predictive models. This is the basis for the environmental health risk assessment strategy of ARPA. The priority activity areas for ARPA are: urban areas, environmental and health effects of traffic (atmospheric pollution and noise pollution); industrial areas (Ravenna chemical plants, Modena/Reggio-Emilia ceramic factories and Ferrara chemical plants); high-speed trains; pesticides; asbestos; and pollution of the Adriatic Sea.**

INTRODUCTION

In the past 20 years there has been growing interest in the environment and quality of life in Italy. One effect has been the creation and development of public environmental health preventive services. As a result of a referendum held in 1993. 1994 the national and regional Environmental Protection Agencies network was tablished, engaging personnel from environmental and health laboratories, and fr National Health Services. This rearrangement offered an opportunity to reconsi environmental and health prevention services in the Emilia-Romagna region wh these services had been established in the 1970s and 1980s. At present, 15 out of Italian regions have legislated environmental agencies, although not all of these h as yet been constituted, see FIGURE 1.

FEATURES OF ARPA EMILIA-ROMAGNA

ARPA Emilia-Romagna has adopted the following *mission*: "To conduct envir mental controls oriented towards general prevention and safeguarding of natural sources and health so as to guarantee ongoing social and economic developmen

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ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

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UNCERTAINTY IN THE RISK ASSESSMENT OF ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

AN INTERNATIONAL WORKSHOP[a]

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